Isolated nocturnal and isolated daytime hypertension associate with altered cardiovascular morphology and function in children with chronic kidney disease: findings from the Cardiovascular Comorbidity in Children with Chronic Kidney Disease study

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Abstract: INTRODUCTION Prevalence of isolated nocturnal hypertension (INH) and isolated daytime hypertension (IDH) is around 10% in adults. Data in children, especially in chronic kidney disease (CKD), are lacking. The aim of this cross-sectional multicenter cohort study was to define the prevalence of INH and IDH and its association with cardiovascular morphology and function, that is, pulse wave velocity (PWV), carotid intima-media thickness (cIMT), or left ventricular mass index (LVMI) in children with CKD. METHODS Ambulatory blood pressure (BP) monitoring profiles were analyzed in 456 children with CKD stages III-V participating in the Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study (64.3% males, 71.3% congenital anomaly of the kidney and urinary tract, age 12.5 ± 3.2 years, estimated glomerular filtration rate 29 ± 12 ml/min per 1.73 m). Baseline PWV, cIMT, and LVMI were compared in normotension, INH, IDH, or sustained 24-h hypertension. RESULTS Prevalence of sustained hypertension was 18.4%, of INH 13.4%, and of IDH 3.7%. PWV SDS (SD score) and cIMT SDS were significantly higher in sustained hypertension and INH, and PWV SDS was significantly higher in IDH, compared with normotension. LVMI was significantly increased in sustained hypertension, but not in INH or IDH. Determinants of INH were smallness for gestational age, older age, higher height SDS and parathyroid hormone, and shorter duration of CKD. In logistic regression analysis, day/night-time hypertension or ambulatory BP monitoring pattern (normal, INH, IDH, sustained hypertension) were independently associated with cardiovascular outcome measures: elevated night-time BP was associated with increased cIMT, PWV, and left ventricular hypertrophy; INH was associated with cIMT. CONCLUSION INH is present in almost one out of seven children with predialysis CKD; INH and nocturnal hypertension in general are associated with alterations of arterial morphology and function.

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Original Article

Isolated nocturnal and isolated daytime hypertension associate with altered cardiovascular morphology and function in children with chronic kidney disease: findings from the Cardiovascular Comorbidity in Children with Chronic Kidney Disease study

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Introduction: Prevalence of isolated nocturnal hypertension (INH) and isolated daytime hypertension (IDH) is around 10% in adults. Data in children, especially in chronic kidney disease (CKD), are lacking. The aim of this cross-sectional multicenter cohort study was to define the prevalence of INH and IDH and its association with cardiovascular morphology and function, that is, pulse wave velocity (PWV), carotid intima–media thickness (cIMT), or left ventricular mass index (LVMI) in children with CKD.

Methods: Ambulatory blood pressure (BP) monitoring profiles were analyzed in 456 children with CKD stages III–V participating in the Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study (64.3% males, 71.3% congenital anomaly of the kidney and urinary tract, age 12.5 ± 3.2 years, estimated glomerular filtration rate 29 ± 12 ml/min per 1.73 m^2). Baseline PWV, cIMT, and LVMI were compared in normotension, INH, IDH, or sustained 24-h hypertension.

Results: Prevalence of sustained hypertension was 18.4%, of INH 13.4%, and of IDH 3.7%. PWV SDS (SD score) and cIMT SDS were significantly higher in sustained hypertension and INH, and PWV SDS was significantly higher in IDH, compared with normotension. LVMI was significantly increased in sustained hypertension, but not in INH or IDH. Determinants of INH were smallness for gestational age, older age, higher height SDS and parathyroid hormone, and shorter duration of CKD. In logistic regression analysis, day/night-time hypertension or ambulatory BP monitoring pattern (normal, INH, IDH, sustained hypertension) were independently associated with cardiovascular outcome measures: elevated night-time BP was associated with increased cIMT, PWV, and left ventricular hypertrophy; INH was associated with cIMT.

Conclusion: INH is present in almost one out of seven children with predialysis CKD; INH and nocturnal hypertension in general are associated with alterations of arterial morphology and function.

Keywords: ambulatory blood pressure monitoring, carotid intima–media thickness, chronic kidney disease, isolated daytime hypertension, isolated nocturnal hypertension, left ventricular hypertrophy, left ventricular mass index, pulse wave velocity

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Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CAKUT, congenital anomaly of the kidney and urinary tract; cIMT, carotid intima–media thickness; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HTN, hypertension; IDH, isolated daytime hypertension; INH, isolated nocturnal hypertension; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; PTH, parathyroid hormone; PWV, pulse wave velocity; SDS, standard deviation score; SGA, smallness for gestational age

INTRODUCTION

Children with chronic kidney disease (CKD) are at high risk for cardiovascular morbidity and mortality. Cardiovascular disease accounts for the majority of deaths in adults and approximately one quarter of deaths in children with end-stage renal disease (ESRD) [1]. In young adults with ESRD, cardiovascular mortality is increased up to 1000-fold compared with the general population [2]. Uncontrolled hypertension (HTN) is a risk factor for cardiovascular morbidity and for progression of CKD in adults [3,4].

High blood pressure (BP) is also a predictor of renal disease progression in children with CKD [5]. The prevalence of HTN in children with CKD Stages II–IV is 25–50% in reports from the North American Pediatric Renal Trials and Collaborative Studies, the CKD in Children (CKiD) Study, and the Effect of Strict Blood Pressure Control and ACE Inhibition on Chronic Renal Failure Progression in Pediatric Patients (ESCAPE) trial group [6–8]. Ambulatory BP monitoring (ABPM) is superior to conventional office or home BP monitoring in assessing BP load and stratifying cardiovascular risk, particularly in CKD patients [9].

Li *et al.* [10] identified a group of individuals who had abnormally elevated night-time BP but normal daytime BP in ABPM; they defined this BP pattern as isolated nocturnal hypertension (INH). INH was associated with clustering of cardiovascular risk factors, thickening of carotid intima–media, left ventricular (LV) remodeling and increased arterial stiffness in adult patients with essential HTN or type 2 diabetes mellitus who had well controlled self-measured home daytime BP [10–12]. In a population-based cohort study in African-American adults, INH was associated with increased LV mass [13].

In a meta-analysis of 8711 adults from 10 populations, INH predicted cardiovascular outcome in patients who were normotensive based on office or ambulatory daytime BP measurements [14].

In adolescents and young adults with diabetes mellitus type 1, an increase in SBP during sleep preceded the development of microalbuminuria [15]. In a pediatric outpatient clinic, patients (6–18 years old) with persistent masked HTN, defined as an elevated daytime ambulatory BP in the presence of a normal office BP, had higher LV mass index than normotensive controls [16].

So far, no data have been published on the prevalence of isolated daytime hypertension (IDH) and its impact on cardiovascular health in children.

Here, we aimed to define the prevalence and determinants of INH and IDH, and to evaluate potential associations of INH and IDH with cardiac and vascular morphology and function in children with CKD stages III–V. For this purpose, we analyzed data from the Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study, a prospective cohort study in nearly 700 European children designed to evaluate the causes and consequences of cardiovascular comorbidity of progressive CKD in childhood and adolescence.

METHODS

Study population

The 4C Study enrolled 688 patients, aged 6–17 years, with predialysis CKD stages III–V at 55 pediatric nephrology centers in 12 European countries between October of 2009 and August of 2011 (17). Patients with active systemic vasculitis, diabetes mellitus, renal vascular anomalies, anomalies of the limbs preventing standardized diagnostic procedures, and relevant CKD-unrelated cardiovascular anomalies were excluded. The study was approved by all local ethical committees and conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was given by the parents and adolescents, and oral assent by younger children [17].

All children are followed prospectively with 6-monthly clinical assessments, blood and urine collection. ABPM, pulse wave velocity (PWV), carotid intima–media thickness (cIMT), and echocardiographic measurements are performed annually. For the present cross-sectional study, the clinical information and laboratory data at the time of first valid ABPM in predialysis CKD patients were analyzed.

Definitions

Renal diagnoses were categorized as CAKUT (congenital anomaly of the kidney and urinary tract), glomerulopathies, CKD following acute kidney injury, tubulointerstitial diseases, and other or unknown. Physical activity score was estimated by hours of physical activity (0, 1–2, 3–4, >4 h/week) using a standardized questionnaire [17,18].

Standardized height (height SDS, SD score) and BMI (SDS) were calculated from the WHO Child Growth Standards [19]. SD score (SDS or *z*-score) indicates how many SDs an observation is above or below the mean/median. Office BP values were standardized according to the algorithm published in the Fourth Report [20].

Laboratory measurements

A centralized routine laboratory analysis was performed including creatinine, cystatin C, urea, high sensitivity C-reactive protein (hsCRP), albumin, lipid levels, calcium, phosphate, and parathyroid hormone (PTH) as described elsewhere [21]. Hemoglobin (Hb) levels were measured locally. Estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) was calculated from creatinine, cystatin C, urea, and height according to a published equation [22]. CKD stage was defined by eGFR according to Kidney Disease Outcomes Quality Initiative guidelines [23].

Ambulatory blood pressure monitoring measurements

ABPM measurements, performed on regular school days, were taken using the Spacelabs Monitor 90207 or 90217 device (Spacelabs Healthcare, Snoqualmie, Washington, USA) with the most appropriate sized cuff applied on the nondominant arm. Readings were taken every 15–20 min during the day and every 30–45 min at night [24]. A valid ABPM profile was defined by at least 18 h of continuous recording and at least 20 valid daytime (awake) measurements and at least seven at night (asleep) (based on the requirement to have at least 70% of measurements being obtained every 30 min, or more frequently, throughout the entire 24-h period) *and* at least one valid reading per hour, including night-time, as a primary criterion for an interpretable study [25,26]. A total of 456 profiles of a total of 545 ABPM profiles available (83.7%) met these quality criteria and were included in the analysis.

The age and sex-specific SDS was calculated for each patient's mean BP according to Wühl *et al.* [24]. For the purpose of this study ABPM profiles were classified as follows:

(1) Normal ABPM profile (normal-BP) was defined as daytime (0800 to 2000 h) *and* night-time (midnight to 0600 h) SBP *and* DBP less than 95th percentile.
(2) Daytime HTN was defined as daytime SBP and/or DBP at least 95th percentile.
(3) Night-time HTN was defined as night-time SBP and/or DBP at least 95th percentile.
(4) Sustained hypertension was defined as daytime *and* night-time SBP and/or DBP at least 95th percentile.
(5) INH was defined as daytime SBP and DBP less than 95th percentile and night-time SBP and/or DBP at least 95th percentile.
(6) IDH was defined as daytime SBP and/or DBP at least 95th percentile and night-time SBP and DBP less than 95th percentile.

Definitions for white-coat HTN, masked HTN, BP load and dipping are given in Supplementary material [27] (additional definitions for ABPM, http://links.lww.com/HJH/B112).

Left ventricular mass index

Standard echocardiographic measurements of the left ventricle were performed. All echocardiographs are evaluated and analyzed by a core lab [17,18]. The LV mass (LVM) was determined following the modified Devereux formula [28]. LVM index (LVMI) was calculated according to Chinali *et al.* [29] [$\text{LVMI} = \text{LVM}/(\text{height}^{2.16} + 0.09)$]. A partition value of $45\,\text{g/m}^{2.16}$ was defined as the upper normal limit for LVMI.

Carotid intima–media thickness

Ultrasound examination was performed according to the Mannheim carotid intima–media thickness consensus [30] using an 8-MHz annular array ultrasound imaging system (Siemens Acuson P50 Ultrasound system, Software version 2.1; Siemens Medical Solution USA, Inc. Mountain View, California, USA) with integrated digital image evaluation software (Syngo US Workplace, Siemens Medical Solutions, USA Inc., Ann Arbor, Michigan, USA). cIMT was obtained either by five averaged measurements on each side or semiautomatically using a digital image evaluation software. All values were transformed to SDS adjusted for height and sex using reference values established by our group [31].

Aortic pulse wave velocity

Aortic PWV was assessed using the oscillometric Vicorder device (SMT medical, Würzburg, Germany) using the distance from the suprasternal notch to the femoral recording point via the umbilicus as path length. Settings and measurement conditions were as previously reported [32,33]. Description of the measurements are summarized in Supplementary material (Description of aortic PWV measurements, http://links.lww.com/HJH/B112). The measured values were transformed to SDS adjusted for height and sex using reference values established by our group [33].

Statistics

Normally distributed continuous data were summarized by the mean ± SD, and nonnormally distributed variables were summarized by the median and interquartile range (IQR). Categorical variables were presented as number and percentages and compared by using Chi-square or Fisher's exact test. One-way analysis of variance test or Kruskal–Wallis test was used to compare continuous data between the four ABPM groups, as appropriate; pairwise comparisons (*t* test or Mann–Whitney *U* test) were performed when there was a statistically significant difference between the groups (main effect). Logistic regression analyses were performed to define independent risk factors for INH (reference: normotension); variables associated by univariate analysis at *P* of 0.20 or less were further entered into the logistic regression analysis. Logistic regression analyses were performed to evaluate whether daytime hypertension, nighttime hypertension, and ABPM patterns (i.e. normal ABPM, INH, IDH, and sustained hypertension) were independently associated with LV hypertrophy, elevated cIMT (≥95th percentile for sex and height) and PWV (≥95th percentile for sex and height). Variables associated by univariate analysis at *P* of 0.20 or less were further entered into the logistic regression analysis. Two models which included daytime / night-time HTN (Model A) or type of ABPM profiles (Model B) were evaluated. In model A, the presence of daytime (including IDH and sustained hypertension) and night-time HTN (including INH and sustained hypertension) was studied, the reference was normotension during daytime or night-time, respectively. In model B, the presence of INH, IDH or sustained hypertension was studied, the reference was normal 24-h ABPM. Hosmer–Lemeshow goodness of fit statistics were used to assess model fit. *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed with the SPSS version 22.0 package program for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Four-hundred fifty-six children with CKD stages III–V (64.3% males, 71.3% CAKUT, mean age 12.5 ± 3.2 years, eGFR 29 ± 12 ml/min/1.73 m^2) were included in the analysis. ABPM revealed normal BP throughout day and night in

TABLE 1. Clinical characteristics of the patients according to ambulatory blood pressure monitoring groups

Patient characteristics	ABPM groups					*P*
	Normotension, *N* = 294	INH, *N* = 61	IDH, *N* = 17	SH, *N* = 84	Total, *N* = 456	
Male, *N* (%)	194 (66.0)	39 (63.9)	10 (58.8)	34 (59.5)	293 (64.3)	0.700*
Age (years)**	12.6 (5.4)	13.8 (5.2)	12.4 (4.7)	11.8 (4.6)	12.5 (5.2)	0.127**
Height SDS**	−1.32 (1.84)	−1.02 (1.58)	−1.50 (1.69)	−1.41 (1.25)	−1.32 (1.64)	0.110**
BMI SDS**	0.18 (1.58)	0.02 (2.20)	0.67 (1.85)	0.01 (1.31)	0.11 (1.59)	0.447**
CKD duration (months)**	70.4 (91.0)[a,b]	44.6 (85.3)[a]	59.7 (85.1)	41.6 (57.9)[b]	58.6 (85.6)	**<0.001**
Underlying disease, *N* (%)						
CAKUT	216 (73.5)	39 (63.9)	11 (64.7)	59 (70.2)	325 (71.3)	0.440*
Glomerulopathy	18 (6.1)	2 (3.3)	1 (5.9)	6 (7.1)	27 (5.9)	0.793***
Post-AKI CKD	14 (4.8)	2 (3.3)	1 (5.9)	2 (2.4)	19 (4.2)	0.687***
Tubulointerstitial diseases	29 (9.9)	13 (21.3)	3 (17.6)	10 (11.9)	55 (12.1)	0.080*
Other or unknown	24 (8.2)	7 (11.5)	1 (5.9)	7 (8.3)	39 (8.6)	0.848*
Physical activity, *N* (%)						
0 h/week	58/286 (20.3)	30/58 (34.5)	7/17 (41.2)	26/81 (32.1)	111/442 (25.1)	
1–2 h/week	47/286 (16.4)	8/58 (13.8)	0/17 (0)	10/81 (12.3)	65/442 (14.7)	
3–4 h/week	25/286 (8.7)	5/58 (8.6)	2/17 (11.8)	6/81 (7.4)	38/442 (8.6)	
>4 h/week	156/286 (54.5)	25/58 (43.1)	8/17 (47.1)	39/81 (48.1)	228/442 (51.6)	
≥1 h/week	228/286 (79.7)[a,b]	38/58 (65.5)[a]	10/17 (58.8)	55/81 (67.9)[b]	331/442 (74.9)	0.013*
CKD Stage, *n/N* (%)						
Stage III	120/293 (40.9)	28/61 (45.9)	7/15 (41.2)	27/84 (32.2)	182/455 (40.0)	0.371*
Stage IV	157/293 (53.6)	29/61 (47.5)	8/15 (47.1)	44/84 (52.4)	238/455 (52.3)	0.830*
Stage V	16/293 (5.5)[b]	4/61 (6.6)	2/15 (11.8)	13/84 (15.5)[b]	35/455 (7.7)	**0.021****
eGFR (ml/min per 1.73 m^2)**	27.0 (15.3)	28.6 (14.7)	29.0 (20.8)	24.0 (16.2)	26.9 (15.3)	0.360**
Albuminuria (mg/g creatinine)**	264 (857)[a,b,c]	487 (1960)[a]	774 (1157)[c]	1224 (2401)[b]	368 (1196)	**<0.001****

ABPM, ambulatory blood pressure monitoring; AKI, acute kidney injury; CAKUT, congenital anomalies of kidney and urinary tract; eGFR, estimated glomerular filtration rate; IDH, isolated daytime hypertension; INH, isolated nocturnal hypertension; IQR, interquartile range; SDS, SD score; SH, sustained hypertension.
Bold values represent a *P* value < 0.05.
[a]Statistically significant difference between normal and INH.
[b]Statistically significant difference between normal and SH.
[c]Statistically significant difference between normal and IDH.
*Chi-square test is used to compare four ABPM groups.
**Values are shown as median (IQR); Kruskal–Wallis test is used to compare four ABPM groups; Mann–Whitney *U* test is performed for pairwise comparisons when there is a statistically significant difference between four groups (main effect).
***Fisher's exact test is used to compare four ABPM groups.

294 children (64.5%), sustained hypertension in 84 children (18.4%), INH in 61 children (13.4%), and IDH in 17 children (3.7%).

Three hundred and twenty-six patients (71.5%) had normal casual BP; among those, the fractions of patients with normal ABPM, INH, IDH, and sustained hypertension were 74.8% ($n = 244$), 14.4% ($n = 47$), 2.5% ($n = 8$), and 8.3% ($n = 27$), respectively (Supplement Table 1, http://links.lww.com/HJH/B112). Accordingly, 82 children (18%) had masked hypertension and 50 children (11%) displayed white coat HTN, respectively.

The clinical characteristics of patients with normal ABPM, INH, and sustained hypertension are shown in Table 1. The groups were comparable for sex, age, height, BMI, underlying renal disease distribution, prevalence of prematurity, low birth weight, and smallness for gestational age (SGA). Median CKD vintage was significantly longer in the normal ABPM [70.4 (IQR 91.0) months; $P < 0.001$] compared with the INH [44.6 (IQR 85.3) months] and sustained hypertension patients [41.6 (IQR 57.9) months]. Physical activity at least 1 h/week was more common in children with normal ABPM; and CKD stage 5 was more common in the sustained hypertension group. Albuminuria was lower in the children with normal ABPM. The groups differed with respect to inorganic serum phosphorus, and PTH level, whereas Hb, albumin, lipid, and hsCRP were comparable (Supplement Table 2, http://links.lww.com/HJH/B112).

The mean daytime, night-time and 24-h mean arterial blood pressure (MAP) values, load and dipping and fraction of nondippers by group are presented in Table 2 and additional information for SBP and DBP variables are given in Supplement Table 3, http://links.lww.com/HJH/B112. Although the fraction of patients receiving antihypertensive therapy and the mean number of antihypertensive drugs were comparable, significantly more patients with sustained hypertension received calcium channel blockers compared with patients with controlled HTN (Table 2).

In the INH group, daytime BP was within the normal range, but significantly higher compared with normotensive patients (MAP SDS 0.60 vs. −0.42, $P < 0.001$), by definition nocturnal BP was significantly elevated. In the IDH group, daytime BP was significantly elevated, but nocturnal BP did not differ from the normotensive group. Sustained hypertension patients had significantly higher day and night-time MAP SDS values compared with both IDH and INH (Table 2).

24-h BP load was lower in INH (41.2%; probably due to the shorter night period; 6 h) than in IDH patients (59.2%; $P = 0.006$); in both groups 24-h BP load was significantly lower compared with sustained hypertension (83.0%; $P < 0.001$).

The fractions of patients receiving their antihypertensive medications during day or evening hours and the fractions of patients on single daily dose did not differ significantly between the ABPM phenotypes (Supplement Table 4,

TABLE 2. Office blood pressure and ambulatory blood pressure monitoring findings and use of antihypertensive drugs of the patients according to ambulatory blood pressure monitoring groups

Parameters	ABPM groups					*P*
	Normotension, *N* = 294	INH, *N* = 61	IDH, *N* = 17	SH, *N* = 84	Total, *N* = 456	
Office BP						
Office SBP (mmHg)*	110 (17)[a,b,c]	110 (17)[a,d]	120 (20)[b]	120 (18)[c,d]	110.0 (20)	**<0.001***
Office SBP SDS*	0.40 (1.46)[a,b,c]	0.64 (1.46)[a,d,e]	1.57 (1.80)[b,e]	2.03 (1.62)[c,d]	0.65 (1.73)	**<0.001***
Office SBP >95th pct, *N* (%)	41 (14)[b,c]	12 (20)[d]	7 (41)[b]	51 (62)[c,d]	111 (24.3)	**<0.001****
Office DBP (mmHg)*	65.0 (10)[b,c]	69.0 (16)[d,e]	78.0 (24)[b,e]	80.0 (18)[c,d]	68 (17)	**<0.001***
Office DBP SDS*	0.23 (1.05)[a,b,c]	0.38 (1.13)[a,d,e]	1.33 (2.06)[b,e]	1.72 (1.47)[c,d]	0.49 (1.41)	**<0.001***
Office DBP >95th pct, *N* (%)	24 (8.2)[b,c]	6 (9.8)[d,e]	7 (41.2)[b,e]	44 (52.4)[c,d]	81 (17.8)	**<0.001****
ABPM						
Day MAP (mmHg)*	83.8 (10)[a,b,c]	91.2 (6)[a,d,e]	98.0 (7)[b,e,f]	102.9 (11)[c,d,f]	88.1 (13)	**<0.001***
Day MAP SDS*	−0.42 (1.33)[a,b,c]	0.60 (0.91)[a,d,e]	1.83 (1.07)[b,e,f]	2.67 (1.91)[c,d,f]	0.22 (2.0)	**<0.001***
Day MAP load (%)*	6.67 (16)[a,b,c]	23.5 (32)[a,d,e]	60.6 (32)[b,e]	76.8 (36)[c,d]	14.0 (40)	**<0.001***
Night MAP (mmHg)*	73.3 (8)[a,b,c]	83.2 (6)[a,d,e]	77.3 (3)[b,e,f]	92.4 (12)[c,d,f]	77.0 (11)	**<0.001***
Night MAP SDS*	0.39 (1.33)[a,b,c]	1.97 (0.87)[a,d,e]	1.01 (0.47)[b,e,f]	3.09 (1.83)[c,d,f]	0.91 (1.87)	**<0.001***
Night MAP load (%)*	8.33 (25)[a,b,c]	63.64 (26)[a,d,e]	27.78 (24)[b,e,f]	100.0 (23)[c,d,f]	25 (64)	**<0.001***
24-h MAP (mmHg)*	81.2 (8)[a,b,c]	88.7 (6)[a,d,e]	91.8 (8)[b,e,f]	100.0 (12)[c,d,f]	85.0 (12)	**<0.001***
24-h MAP SDS*	−0.12 (1.33)[a,b,c]	1.18 (0.86)[a,d,e]	1.72 (1.25)[b,e,f]	3.28 (1.97)[c,d,f]	0.52 (2.06)	**<0.001***
24-h MAP load (%)*	13.5 (22)[a,b,c]	41.2 (24)[a,d,e]	59.2 (25)[b,e,f]	83.0 (28)[c,d,f]	27.3 (46)	**<0.001***
MAP dipping (mmHg)***	12.9 ± 5.7[a,b,c]	7.1 ± 4.7[a,d,e]	22.0 ± 3.4[b,e,f]	10.8 ± 6.8[c,d,f]	12.1 ± 6.3	**<0.001*****
MAP nondipper, *N* (%)	86 (29.3)[a,b]	42 (68.9)[a,d,e]	0 (0)[b,e,f]	34 (40.5)[d,f]	162 (35.5)	**<0.001****
Number of AHT*	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0.818*
AHTs (yes), *N* (%)	126 (42.9)	26 (42.6)	7 (41.2)	41 (48.8)	200 (43.9)	0.791**
ACE-i	99 (33.7)	17 (27.9)	5 (29.4)	20 (23.8)	141 (30.9)	0.345**
ARB	23 (7.8)	3 (4.9)	1 (5.9)	3 (3.6)	30 (6.6)	0.534****
CCB	31 (10.5)[c]	11 (18.0)	3 (17.6)	24 (28.6)[c]	69 (15.1)	0.001**
Beta blockers	8 (2.7)	4 (6.6)	0 (0)	4 (4.8)	16 (3.5)	0.349****

ABPM, ambulatory blood pressure monitoring; ACE-i, angiotensin converting enzyme inhibitors; AHT, antihypertensive drug; ARB, AT1 blockers; CCB, calcium channel blockers; INH, isolated nocturnal hypertension; IQR, interquartile range; MAP, mean arterial blood pressure; SDS, SD score; SH, sustained hypertension.
Bold values represent a *P* value < 0.05.
[a]Statistically significant difference between normal and INH.
[b]Statistically significant difference between normal and IDH.
[c]Statistically significant difference between normal and SH.
[d]Statistically significant difference between INH and SH.
[e]Statistically significant difference between INH and IDH.
[f]Statistically significant difference between IDH and SH.
*Values are shown as median (IQR); Kruskal–Wallis test is used to compare four ABPM groups; Mann–Whitney *U* test is performed for pairwise comparisons when there is a statistically significant difference between four groups (main effect).
**Chi-square test is used to compare four ABPM groups.
***Values are shown as mean ± SD; one-way analysis of variance (ANOVA) test is used to compare four ABPM groups; *t* test is performed for pairwise comparisons when there is a statistically significant difference between four groups (main effect).
****Fisher's exact test is used to compare four ABPM groups.

http://links.lww.com/HJH/B112). Load and dipping data for daytime, night-time and 24-h were comparable among treated and untreated normotensive patients (data not shown).

Presence of SGA, older age, higher height SDS and PTH, and shorter duration of CKD were independent determinants of INH (Table 3).

Cardiovascular measures

PWV SDS, cIMT SDS, and LVMI were higher in sustained hypertension compared with patients with normal ABPM ($P < 0.001$) (Table 4, Fig. 1a–c). In patients with INH PWV SDS and cIMT SDS were also higher compared with normal ABPM ($P < 0.05$), whereas the difference in LVMI did not reach statistical significance.

TABLE 3. Independent risk factors for isolated nocturnal hypertension (reference: normotension)

Risk factors	OR	95% CI	*P*
Age (year)	1.148	[1.030; 1.280]	0.013
SGA (vs. normal)	2.613	[1.194; 5.717]	0.016
Height SDS	1.507	[1.149; 1.976]	0.003
CKD duration (months)	0.992	[0.986; 0.998]	0.010
Office SBP SDS	1.285	[0.995; 1.660]	0.055
PTH (pmol/l)	1.012	[1.001; 1.023]	0.027

CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; PTH, parathyroid hormone; SDS, SD score; SGA, smallness for gestational age.

A subgroup analysis considering the use of antihypertensive agents (AHT) did not show any significant effect on cardiovascular measures in general, but PWV SDS in the normal ABPM group with AHT was significantly lower compared with the normal ABPM group without AHT (-0.51 ± 1.64 vs. 0.15 ± 1.39; $P < 0.001$; Supplement Table 5, http://links.lww.com/HJH/B112).

BP pattern over 24 h correlated with the cumulative number of cardiovascular abnormalities (Fig. 2; $r = 0.275$, $P < 0.001$). The fraction of patients with two or more cardiovascular abnormalities was higher in the INH group (14/42; 33.3%) compared with patients with normal ABPM findings (36/215; 16.7%; $P = 0.013$), but lower than in sustained hypertension patients (24/57; 42.1%; $P = 0.375$). The fraction of patients with two or more cardiovascular abnormalities was not significantly different in the IDH group (4/16; 25.0%) compared with patients with normal ABPM findings (36/215; 16.7%; $P = 0.40$, Fisher's exact test), and in sustained hypertension patients (24/57; 42.1%; $P = 0.214$).

TABLE 4. Cardiovascular measures according to ambulatory blood pressure monitoring groups

	ABPM groups				*P*
	Normal	INH	IDH	SH	
PWV (m/s)*	4.67 (1.00)[a,b,c] ($n=223$)	4.93 (1.00)[a] ($n=45$)	4.97 (1.00)[b] ($n=16$)	5.21 (1.00)[c] ($n=62$)	**<0.001***
PWV SDS**	-0.13 ± 1.54[a,b,c] ($n=223$)	0.55 ± 1.42[a,d] ($n=45$)	0.85 ± 1.51[b] ($n=16$)	1.38 ± 1.94[c,d] ($n=62$)	**<0.001****
Elevated PWV, *N* (%)	27/223 (12.1)[a,c]	11/45 (24.4)[a,d]	4/16 (25.0)	30/62 (48.4)[c,d]	**<0.001*****
cIMT (mm)*	0.45 (0.08)[a,c] ($n=225$)	0.47 (0.08)[a] ($n=44$)	0.47 (0.07) ($n=16$)	0.46 (0.09)[c] ($n=60$)	**0.012***
cIMT SDS*	1.44 (1.60)[a,c] ($n=225$)	1.72 (1.67)[a] ($n=44$)	1.71 (1.70) ($n=16$)	1.94 (2.06)[c] ($n=60$)	**0.001***
Elevated cIMT, *N* (%)	93/225 (41.3)	25/44 (56.8)	8/16 (50.0)	33/60 (55.0)	0.104***
LVM (g)*	87.5 (45.1) ($n=223$)	96.8 (53.7) ($n=45$)	99.0 (44.9) ($n=16$)	85.2 (52.4) ($n=63$)	0.313*
LVMI [$g/(m^{2.16}+0.09)$]*	39.7 (15.8)[c]	41.2 (20.1)	44.1 (17.8)	47.4 (19.4)[c]	**<0.001***
LV hypertrophy, *N* (%)	71/223 (31.8%)[c]	19/45 (42.2)	7/16 (43.8)	36/63 (57.1)[c]	**0.003*****

PWV, cIMT, and LVM/LVMI measurements were available in 346, 345, and 347 patients, respectively. ABPM, ambulatory blood pressure monitoring; cIMT, carotid artery intima–media thickness; IDH, isolated daytime hypertension; IQR, interquartile range; INH, isolated nocturnal hypertension; LVM, left ventricular mass; LVMI, left ventricular mass index; PWV, pulse wave velocity; SH, sustained hypertension.
Bold values represent a *P* value < 0.05.
[a]Statistically significant difference between normal and INH.
[b]Statistically significant difference between normal and IDH.
[c]Statistically significant difference between normal and SH.
[d]Statistically significant difference between INH and SH.
*Values are shown as median (IQR); Kruskal–Wallis test is used to compare four ABPM groups; Mann–Whitney *U* test is performed for pairwise comparisons when there is a statistically significant difference between four groups (main effect).
**Values are shown as mean ± SD; one-way analysis of variance (ANOVA) test is used to compare four ABPM groups; *t* test is performed for pairwise comparisons when there is a statistically significant difference between four groups (main effect).
***Chi-square test is used to compare four ABPM groups.

In multivariable analyses, night-time HTN (Model A) and type of ABPM profiles (Model B) remained significantly associated with left ventricular hypertrophy (LVH), elevated cIMT and elevated PWV (Table 5). Nocturnal HTN independently predicted the risk of LVH and elevated cIMT and PWV.

Presence of sustained hypertension was predictive for LVH and higher PWV, while INH was predictive for the risk of elevated cIMT only and IDH was not predictive for cardiovascular risk in the logistic regression model.

DISCUSSION

This is the first study to compare the prevalence and relationship of INH and IDH with cardiovascular morbidity in children with predialysis CKD stages III–V. Sustained hypertension, INH and IDH were identified in 18.4, 13.4 and 3.7% of patients, respectively. In the general adult population INH has been reported in 6–11% and IDH in 5–14%, with slightly higher rates observed among Europeans compared with Asians and Africans [10]. The prevalence of INH and IDH among healthy children is unknown. In adults with CKD, a recent study from China reported sustained hypertension, INH and IDH prevalence of 50.8, 20.4 and 1.5%, respectively [34]. Hence, the prevalence of INH in children with CKD appears to range between the general adult population and adult CKD patients. The lower frequency of IDH observed in CKD patients compared with the general population is probably attributable to their higher frequency of INH and sustained hypertension.

We identified by multivariate analysis a history of SGA, older age, shorter duration of CKD, higher height SDS and hyperparathyroidism as risk factors for INH. The observed association of SGA with INH is in keeping with previous findings in pediatric non-CKD populations and suggests that a selective upregulation of nocturnal BP may be an early sign of the adverse cardiovascular phenotype resulting from reprogramming in response to adverse in-utero conditions [35,36]. Older age, larger standardized height and shorter CKD duration might be related to non-CAKUT diseases, which usually show faster CKD progression. Higher PTH levels are associated with an increased risk for HTN even within the normal PTH range [37]. PTH may increase BP via activation of the renin–angiotensin–aldosterone system,

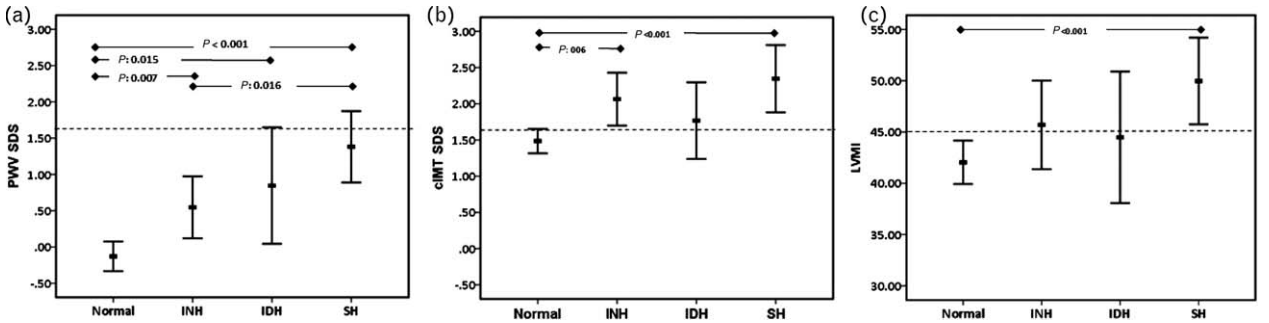

FIGURE 1 Mean pulse wave velocity SD score (a), carotid intima–media thickness SD score (b) and left ventricular mass index (c) values by ambulatory blood pressure monitoring groups. Error bars represent ±2 SEM. Dashed lines represent 95th percentile values for pulse wave velocity SD score and carotid intima–media thickness SD score, and 45 $g/m^{2.16}$ for left ventricular mass index, respectively. ABPM, ambulatory blood pressure monitoring; IDH, isolated daytime hypertension; INH, isolated nocturnal hypertension; SH, sustained hypertension.

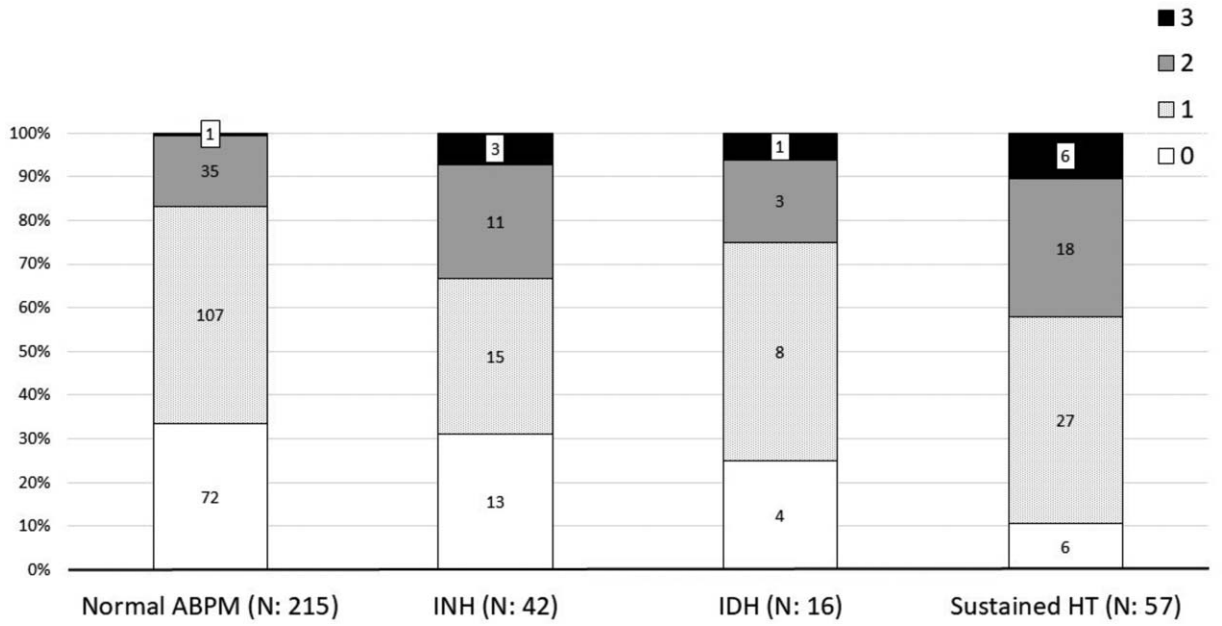

FIGURE 2 Percentages and numbers of patients presenting with zero, one, two, or three abnormal cardiovascular measures by ambulatory blood pressure monitoring groups. ABPM, ambulatory blood pressure monitoring; HT, hypertension; IDH, isolated daytime hypertension; INH, isolated nocturnal hypertension.

TABLE 5. Logistic regression models for cardiovascular outcome (Model A included day/night hypertension; Model B included type of ambulatory blood pressure monitoring profiles, see definitions and statistical analysis for details)

Model A

Variables	LVH			Elevated cIMT			Elevated PWV		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Male sex	2.298	1.338; 3.944	0.003				0.454	0.241; 0.855	0.015
Low birth weight				2.371	1.130; 4.976	0.022			
BMI SDS	1.748	1.388; 2.200	<0.001	1.292	1.049; 1.592	0.016			
Physical activity ≥3 h/week	0.554	0.333; 0.921	0.023	1.965	1.178; 3.278	0.010			
Hemoglobin (g/dl)				0.828	0.706; 0.971	0.020			
Phosphate (mmol/l)							0.309	0.123; 0.780	0.013
LDL (mg/dl)							1.010	1.001; 1.019	0.029
eGFR (ml/min per 1.73 m^2)	0.969	0.947; 0.992	0.009						
Office-SBP SDS							1.764	1.388; 2.243	<0.001
Daytime HT			NS			NS			NS
Night-time HT	2.458	1.434; 4.214	0.001	2.016	1.125; 3.614	0.018	2.959	1.561; 5.608	0.001

Model B

Variables	LVH			Elevated cIMT			Elevated PWV		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Male sex	2.379	1.377; 4.112	0.002				0.466	0.246; 0.883	0.019
Low birth weight				2.491	1.178; 5.267	0.017			
BMI SDS	1.726	1.370; 2.175	<0.001	1.290	1.045; 1.592	0.018			
Physical activity ≥3 h/week	0.551	0.330; 0.919	0.022	1.982	1.184; 3.319	0.009			
Hemoglobin (g/dl)				0.827	0.705; 0.971	0.020			
Phosphate (mmol/l)							0.272	0.105; 0.707	0.008
LDL (mg/dl)							1.009	1.000; 1.018	0.053
eGFR (ml/min per 1.73 m^2)	0.969	0.947; 0.992	0.009						
Office-SBP SDS							1.661	1.296; 2.128	<0.001
ABPM type (ref: normotension)			0.005			0.051			0.004
ABPM-INH	1.820	0.868; 3.815	0.113	2.832	1.170; 6.859	0.021	2.049	0.846; 4.962	0.112
ABPM-IDH	1.662	0.521; 5.295	0.391	2.074	0.672; 6.399	0.205	1.662	0.436; 6.336	0.457
ABPM-SH	3.281	1.682; 6.399	<0.001	1.802	0.895; 3.626	0.099	4.428	1.985; 9.879	<0.001

ABPM, ambulatory blood pressure monitoring; cIMT, carotid artery intima–media thickness; eGFR, estimated glomerular filtration rate; HT, hypertension; IDH, isolated daytime hypertension; INH, isolated nocturnal hypertension; LVH, left ventricular hypertrophy; OR, odds ratio; PTH, parathyroid hormone; PWV, pulse wave velocity; SDS, SD score; SH, sustained hypertension.

impairment of endothelial vasodilatory function and thickening of arterial vessel through its prosclerotic effect on smooth muscle cells [38–40].

Studies in adults have provided solid evidence that INH is associated with cardiovascular risk [11–14]. In a recent meta-analysis including 3657 adult patients, both LVMI and cIMT were higher in patients with nocturnal HTN than in those with nocturnal normotension [41].

Data for children and adolescents is limited. In a study of 82 pediatric patients with type 1 diabetes nocturnal HTN, present in 39% of patients, was associated with increased cIMT [42].

Here we demonstrate for the first time that both PWV and cIMT are higher in children with CKD and INH, compared with those with normal ambulatory BP. The associations of nocturnal HTN with these intermediate cardiovascular endpoints were independent of other clinical and biochemical risk factors. In addition, our study suggests that not only INH but also IDH may associate with markers of early cardiovascular morbidity. Despite its low prevalence, IDH was associated with higher PWV SDS. Likewise, cIMT SDS and LVMI were nominally higher compared with the normotensive group although statistical significance was not reached probably due to the small IDH sample size. Finally, we found albuminuria to be equally elevated with INH, IDH and sustained hypertension as compared with normotensive patients. Taken together, these observations suggest that BP elevation, regardless of the time of day, sustained or not, is a risk factor for the development of target-organ lesions.

It has been speculated that adequate treatment of INH normalizing night-time BP level and restoring nocturnal dipping pattern might have an impact on albuminuria, renal disease progression, and cardiovascular risk. Hermida *et al.* [43] showed that among adult patients with CKD and HTN, taking at least one antihypertensive medication at bedtime improved nocturnal BP control and reduced the risk for cardiovascular events. In our cohort, antihypertensive therapy (medication, dosage, time of medications) was at the discretion of the investigators; we were not able to show an impact of taking at least one antihypertensive medication at bedtime on INH. A prospective, randomized study would be needed to elucidate this question.

Although the major strength of this study is the large number of patients collected in a large multicenter, multinational effort with standardized methodology, the analysis presented here is limited by its cross-sectional design and the diagnosis of INH based on single ABPM profiles. Limited published information is available regarding the reproducibility of INH. In a short-term study, INH showed higher persistence than the diagnosis of a blunted nocturnal BP decline (nondipping) [44]. In a long-term study of 30 patients, INH persisted in 10 individuals whereas 10 subjects developed sustained HTN, two shifted to IDH, and eight became normotensive [10]. Furthermore, the findings of our study might have been influenced by antihypertensive therapy, applied in 44% of the patients, which might attenuate the association of HTN with cardiovascular outcome. Finally, the number of patients with IDH was relatively small and it was not possible to make a subgroups analysis, that is compare INH and IDH, to suggest whether there is a differential effect of night-time hemodynamics on myocardium and vasculature. Cross sectional design of the study did not allow to test whether the changes in PWV and cIMT precede an increase in LVMI.

In conclusion, we demonstrate that the prevalence of INH and IDH in children with CKD prior to dialysis were 13.4 and 3.7%, respectively. INH was independently associated with elevated cIMT; elevated night-time BP in general was associated with elevated PWV, cIMT, and LVH. Whether the changes in PWV and cIMT precede an increase in LVMI and whether adequate treatment of INH might prevent cardiovascular morbidity and renal disease progression remains to be shown by longitudinal data analysis.

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Conflicts of interest

There are no conflicts of interest.

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